



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61L 25/00, A61M 1/02, C07K 14/75	A1	(11) International Publication Number: WO 98/11925 (43) International Publication Date: 26 March 1998 (26.03.98)
(21) International Application Number: PCT/EP97/05104 (22) International Filing Date: 13 September 1997 (13.09.97) (30) Priority Data: MI96A001914 18 September 1996 (18.09.96) IT (71)(72) Applicants and Inventors: TARANTINO, Flavio (IT/IT); Via Gioberti, 30, I-07041 Alghero (IT). BENINCASA, Carlo (IT/IT); Via Bernini, 10, I-20092 Cinisello Balsamo (IT). IANNINI, Rocco (IT/IT); Via Cipriani, 1, I-01037 Ronciglione (IT). RAO, Walter (IT/IT); Piazza Castello, 19, I-27100 Pavia (IT). (74) Agent: RICCARDI, Sergio; Riccardi & Co., Via M. Melloni, 32, I-20129 Milano (IT).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>

(54) Title: PROCESS OF PREPARATION OF AN AUTOLOGOUS FIBRIN GLUE**(57) Abstract**

A process of preparation of autologous fibrin glue for surgical use is disclosed, comprising the steps of taking a sample of blood of the same patient and of concentrating progressively by centrifugation the sample for obtaining a basic product, which when mixed with a starter and other suitable additives produces the fibrin glue ready to be used. A preferred embodiment of the process consists of a closed system using three different plastic bags connected to one another by sealed tubes. More particularly in the first bag the blood sample taken from the patient is collected and mixed with an anticoagulating agent, then separating the plasma from the erythrocytes by centrifugation, said plasma is transferred into the second bag provided with a membrane, where through another centrifugation fibrinogen enriched plasma is separated and transferred to one of the two separated parts forming the third bag, while the other part of the bag contains a thrombin solution, so that by extracting contemporaneously the contents of said two parts and letting them flowing together to a terminal needle, the fibrin glue ready to be used is directly obtained, carrying out a closed system avoiding any contamination of the products.

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"PROCESS OF PREPARATION OF AN AUTOLOGOUS FIBRIN GLUE"

The present invention relates to a process of preparation of autologous fibrin glue for surgical use, and more particularly a closed system process, allowing to obtain fibrin glue ready to be used, avoiding submission of blood or its derivatives to the action of external
5 contaminants.

Fibrin glue of bovine or human origin has been known since a long time and successfully used in different surgical conditions. Fibrin is a substance of proteinic nature and originates from the chemical transformation of fibrinogen, a glycoprotide dissolved in blood plasma with a molecular weight around 320,000 D, that during the coagulation process,
10 through the enzyme thrombin, is organized in a stable fibrous structure, namely the fibrin structure.

Glue obtained from fibrin exerts its action through the rapid and durable connection of various biological components, more particularly tissues such as skin, subcutaneous layers, muscular bundles, vessels, prostheses and organs like liver, spleen, kidney, lung. Moreover
15 this glue can be used as a substitute or integration of the surgical sutures and their waterproofing.

The many surgical uses of this glue arise from its main activities such as adhesive, hemostatic, reparative and filling features. In view of its adhesive activity, said glue is being used in:

- 20 - Filling of spaces generated by décollement of the sinusal endosteum as said glue together with calcium hydroxy apatite stimulates the regeneration of mature bone, particularly for filling bone cysts;
- treatment of liquora fistulae;
- eardrum plastics;
- 25 - connection of parenchymatous tissue in the operations on kidney, liver, spleen, pancreas, lung;
- glueing vascular ends to each other or to prostheses, more particularly as support and waterproofing of sutures;
- connection of peripheral nerves in microsurgery operations, for instance of the brachial
30 plexus;
- glueing of skin grafts, paradontal edges and others.

Furthermore, in all these operations fibrin glue showed haemostatic activity, diminishing intra-and post operation haemorrhage. Such a property resulted useful above all in operations where haemorrhage is favoured by the existence of cavities, in which haemostasis is difficult, such as post-extraction bone cavities for instance in inclusions, cysts, apicotomies, 5 prostatectomies and post-tonsillectomies.

The most commonly used fibrin glue is known under the trade name "Tissucol" and is prepared by cryoprecipitation of bovine or human blood. The industrial preparation of said glue is long and gives a commercially available product of rather high cost.

As state of the art there is also another fibrin glue obtained by concentration of platelets 10 and derivatives, always starting from bovine or human blood.

This origin of the blood causes the preparation of the known fibrin glues to fall within the present highly felt problem of the possibility of transmission of known or unknown viral and other diseases.

Therefore in view of the increasing demand, and in some cases the necessity, of 15 products of autologous origin, an object of the present invention is a process of preparation of autologous fibrin glue for surgical use.

The process of autologous preparation of said fibrin glue allows also not to contravene prohibitions and/or beliefs of ethical and/or religious nature, as it does not use patient's blood but only a chemical compound extracted and separated therefrom.

20 Another object of the invention is a process of production of said fibrin glue which is cheap and allows a rapid preparation of the product that is ready to be used.

Still another object of the present invention is a process of preparation giving the possibility of preparing the basic product of autologous fibrin glue and then freezing said basic product in view of a subsequent use.

25 A further object of the invention is a process allowing to obtain fibrin glue in the quantity required by the case, avoiding risks of excessive dosage, as it is possible to take the patient's blood in a quantity consistent with the amount of autologous fibrin glue that one has to produce.

Thus the present invention refers to a process of preparation of autologous fibrin glue 30 for surgical use characterized by the fact of comprising the steps of:

a) taking a quantity of blood of the same patient, consistent with the amount of fibrin glue

- needed and making it uncoagulable by adding an anticoagulating agent;
- b) placing the now uncoagulable blood sample in a centrifuge test tube and subjecting it to centrifugation for separating the supernatant, consisting mainly of blood plasma;
- c) separating the supernatant by a suitable device provided with a filter;
- 5 d) placing the filtrate in a suitable test tube provided with a filtering membrane and subjecting to centrifugation in a centrifuge adapted to lodge said test tube, so as to obtain the basic product of fibrin glue;
- e) subjecting the basic product to a possible freezing and/or subsequent treatment for obtaining fibrin; and
- 10 f) mixing the basic product obtained by centrifugation or thawed, with a starter to obtain fibrin and with an antifibrinolytic agent to get a proper concentration of the final product.

The features of the process of preparation of autologous fibrin glue according to the invention will be better illustrated in the course of the following detailed description.

Said process refers to the preparation of autologous fibrin glue for surgical use.

- 15 Preferably one takes a quantity of patient's venous blood of 20 ml, that are made uncoagulable by adding an anticoagulating agent, for instance 1 ml sodium citrate, or other anticoagulating agents such as EDTA (ethylene diaminetetracetic acid) or heparin.

The so obtained sample is placed in two test tubes of 10 ml each and centrifuged in a conventional laboratory centrifuge at 2,000 rpm for about 5 minutes.

- 20 This centrifugation gives a first separation of the patient's blood plasma from the particulate blood portion, mainly comprising erythrocytes.

Then the supernatant is taken from the test tube through a filtering device, for instance a syringe having a filter where the pore size is preferably between 0.22 μm and 0.45 μm .

- In order to obtain a further separation of the blood plasma from the remnant particulate
25 portion, said filtrate placed in a test tube is subjected to a further centrifugation preferably at 2,500 rpm for one hour.

- Said test tube is provided with a filtering membrane adapted to filter particles of a size between 80,000 and 300,000 D. Said test tube is placed for said second centrifugation of the above mentioned step d) in a centrifuge for test tubes of 10 ml, but with the head modified so
30 as to lodge test tubes of 50 ml.

The basic product so obtained is essentially constituted by fibrinogen and coagulation

factors and can be transformed into fibrin glue preferably within 12 hours.

The basic product, according to a second embodiment, is frozen for subsequent expected use at -18°C and stored for a maximum period of about 12 months. Said product, after being thawed, must be used preferably within 36 hours. The product, either obtained for immediate
5 use or thawed, is mixed with a starter, preferably commercially available thrombin of animal or human origin, for its transformation into fibrin and contemporaneously and/or subsequently with an antifibrinolytic agent, preferably tranexamic acid, for obtaining autologous fibrin glue of suitable concentration.

A third embodiment of the invention consists in taking little quantities of patient's
10 venous blood, preferably 5 ml, which is rapidly concentrated to obtain little amounts of a very tough preparation ready to be used with the process of the invention.

Although the foregoing embodiments of the process allow to obtain autologous fibrin glue, they require a fair amount of manual operations and are particularly adapted to produce little quantities of fibrin glue for little surgical operations, as they are bound to the use of test
15 tubes, thus samples generally of about 20 ml.

A fourth embodiment of the present invention allows to carry out a process of production of autologous fibrin glue with closed system, so as to produce greater quantities of fibrin glue, sufficient even in case of surgeries of a certain relevance and at the same time reduce manipulations avoiding any exposure of blood or its derivatives to the action of external
20 contaminants.

This closed system essentially comprises three bags, namely a first bag or mother bag where the blood taken from the patient is collected, a second bag provided with a horizontal membrane where plasma ultracentrifugation is effected, and a third bag provided with a vertical diaphragm, from which the ingredients contained in the two bag parts are taken at the
25 same time and meet in a terminal delivery member where the preparation of the fibrin glue is carried out at the same moment of its use.

The closed system will now be described in greater detail, with reference to the illustrative diagram shown in the sole figure of the accompanying drawing.

Clearly the bags and the fittings will be made of the most suitable materials and more
30 particularly of anallergic, perfectly sterile plastics of surgical quality.

Moreover bags and fittings may be made in various standard sizes, for treating

1
standardized blood quantities, for instance suitable to receive samples of 50, 100, 200 ml and so forth.

The process according to the fourth embodiment of the invention comprises the following steps, making reference to the illustrative diagram of the attached drawing:

- 5 a) Through a venous inlet 1 from the patient a sufficient amount of whole blood is taken and flows into the mother bag 2 where it is mixed with the anticoagulating agent (CPD, ACD and the like), contained in the bag;
- b) after having sealed the venous inlet 1 the cell part of the plasma is separated by centrifugation in a centrifuge with oscillating baskets;
- 10 c) by means of a bag squeezer the plasma is delivered to the second bag 3, the connection tube 4 is sealed with a bag thermic welder and the mother bag 2 containing concentrated erythrocytes is detached and removed;
- d) the bag 3 containing the plasma is provided with a horizontal membrane 5 allowing, after a proper centrifugation period at a suitable rpm, to obtain in the upper part 6 of the bag 3 a
15 fibrinogen enriched plasma while in the lower part 7 the ultrafiltrated residue may be taken through a suitable outlet 16;
- e) the fibrinogen enriched plasma is transferred (by gravity in the predetermined quantity) into the third bag 8 and the corresponding connecting tube 9 is sealed with the same technique described at step c). The third bag 8 consists of two parts divided by a vertical diaphragm 10
20 of which one part 11 (where the fibrinogen enriched plasma was transferred) contains a suitable amount of a substance with antifibrinolytic action such as aprotinin, while the other part 12 contains a suitable amount of a solution of thrombin and calcium chloride;
- f) contemporaneous squeezing (manual or through a special device) of the two parts 11, 12 of this last bag 8 allows delivery of the substances contained therein through two plastic
25 connections 13, 14 to a terminal needle 15 allowing the final extemporaneous preparation and use of the fibrin glue ready to be utilized.

It is obviously possible to use, in case it should be necessary, both the concentrated erythrocytes contained in the mother bag 2 and the ultrafiltrate contained in the lower part of the bag 3 provided with the membrane 5.

- 30 It is possible to connect the third bag 8 or other dispenser to the bag 3 provided with the membrane 5 through a defluxion member only shortly before the use of the fibrin glue so as

to avoid that the dispenser is manipulated during the various working phases.

Finally the third bag 8 or the dispenser may be closed with an external envelope and sterilized separately from the rest of the system so that the absolute sterility also to the outside, can be preserved up to the moment of use.

- 5 The quantity of substance with antifibrinolytic action contained in part 11 of the third bag 8, when the substance is aprotinin, is about 3000UIK/ml. The quantity of solution of thrombin and calcium chloride contained in the other part 12 of the third bag 8 is about 50 UI thrombin/ml and 40 μ mols CaCl/ml.

- 10 It is clear that to the process according to the present invention, and to the relevant closed system all those modifications, additions and substitutions of elements may be resorted to, that might appear to a man skilled in the art, without departing however from its spirit and scope, nor falling out from its scope of protection: as defined in the appended claims.

CLAIMS

1. Process of preparation of autologous fibrin glue for surgical use, characterized by the
5 fact of comprising the steps of:
 - a) taking a quantity of blood of the same patient, consistent with the amount of fibrin glue needed and making it uncoagulable by adding an anticoagulating agent;
 - b) placing the now uncoagulable blood sample in a centrifuge test tube and subjecting it to centrifugation for separating the supernatant, consisting mainly of blood plasma;
 - 10 c) separating the supernatant by a suitable device provided with a filter;
 - d) placing the filtrate in a suitable test tube provided with a filtering membrane and subjecting to centrifugation in a centrifuge adapted to lodge said test tube, so as to obtain the basic product of fibrin glue;
 - e) subjecting the basic product to a possible freezing and/or subsequent treatment for
15 obtaining fibrin; and
 - f) mixing the basic product obtained by centrifugation or thawed, with a starter to obtain fibrin and with an antifibrinolytic agent to get a proper concentration of the final product.
2. Process according to Claim 1, characterized in that the blood sample taken from the
20 patient is made uncoagulable by sodium citrate, EDTA (ethylenetetraminoacetic acid) or heparin.
3. Process according to Claim 1, characterized in that the quantity of the blood sample taken from the patient is of 20 ml.
4. Process according to Claim 2, characterized in that the blood taken from the patient is made uncoagulable with a quantity of 1 ml of sodium citrate.
- 25 5. Process according to Claim 1, characterized in that the blood sample is placed in test tubes of 10 ml and subjected to centrifugation at 2000 g for a period of 5 minutes.
6. Process according to Claim 1, characterized in that said filtering device of step c) of the process is a syringe with a filter having a pore size between 0.22 μm and 0.45 μm .
7. Process according to Claim 1, characterized in that said centrifugation of step d) of
30 the process takes place at 2500 g for one hour.
8. Process according to Claim 1, characterized in that said test tube for the centrifugation

of step d) of the process is a test tube having a filtering membrane filtering particles of a size between 80,000 D and 300,000 D.

9. Process according to Claim 1, characterized in that the centrifuge for carrying out step d) of the process has a head modified to lodge test tubes of greater size.

5 10. Process according to Claim 1, characterized in that the centrifugated basic product may be frozen at -18°C for a maximum duration of 12 months.

11. Process according to Claim 1, characterized in that said starter of step d) of the process is commercially available thrombin of animal or human origin.

12. Process according to Claim 1, characterized in that said antifibrinolytic agent of step
10 e) is tranexamic acid.

13. Process according to Claim 1, characterized in that the quantity of the blood sample taken from the patient is 5 ml to obtain a very tough preparation for immediate use.

14. Process of production of autologous fibrin glue with closed system through the use of three different plastic bags connected to one another with sealed tubes, characterized by the
15 following steps:

- in the first bag the blood taken from the patient is collected and mixed with an anticoagulant agent contained in it, then separating plasma from erythrocytes by centrifugation after having sealed the venous inlet;
- the plasma is transferred to the second bag provided with a horizontal membrane and after
20 having sealed the connecting tube, fibrinogen enriched plasma is separated by ultracentrifugation in the upper part of said second bag while the ultrafiltrate residue remains in the lower part;
- the desired quantity of fibrinogen enriched plasma is transferred to one of the two chambers constituting the third bag provided with a vertical diaphragm, where it is mixed with a suitable
25 amount of a substance with antifibrinolytic action, while the other chamber contains a solution of thrombin and calcium chloride, and the connection between said second and third bag is sealed; and
- the contents of the two chambers of said third bag is contemporaneously extracted and meets in a terminal needle, obtaining directly the extemporaneous preparation of the fibrin glue
30 ready to be used.

15. Process according to Claim 14, characterized in that the connecting tubes are sealed

by a bag thermic welder.

16. Process according to Claim 14, characterized in that the substance with antifibrinolytic action is aprotinin at a concentration of about 3000 UIK/ml.

17. Process according to Claim 14, characterized in that the quantity of thrombin
5 contained in the solution of the third bag is about 400 UI/ml and for calcium chloride is 40 μ moles/ml.

18. Process according to Claim 14, characterized in that the concentrated erythrocytes contained in the first bag and the ultrafiltrate contained in the lower part of the second bag may be used for other working operations.

10 19. Process according to Claim 14, characterized in that the third bag or other dispenser may be connected to the second bag, through a defluxion member, shortly before using the fibrin glue in order to avoid their manipulation during the preceding working phases.

20. Process according to Claim 14, characterized in that the third bag or the dispenser are closed with an external envelope and sterilized separately from the rest of the system in
15 order to keep sterility also outside up to the moment of use.

21. Closed system for carrying out the process according to one or more of the preceding claims, characterized in that it comprises three bags connected to one another by sealable connecting tubes, namely:

- a first bag or mother bag provided with a venous inlet, where the blood sample taken from
20 the patient is collected and a first centrifugation is effected to separate plasma from erythrocytes;
- a second bag provided with a horizontal membrane in which the ultracentrifugation of plasma is effected so as to separate fibrinogen enriched plasma in the upper part of the bag while the ultrafiltrated residue is collected in its lower part; and
- 25 - a third bag provided with a vertical diaphragm dividing it in two chambers, in one of which said fibrinogen enriched plasma is transferred and mixed with a substance having antifibrinolytic action, while in the other chamber there is a solution of thrombin and calcium chloride, each chamber of said third bag being provided with a connecting tube meeting in a common terminal dispensing device, so that squeezing contemporaneously the two chambers
30 the contents of the two chambers are mixed and the extemporaneous preparation of the autologous fibrin glue ready to be used is obtained.

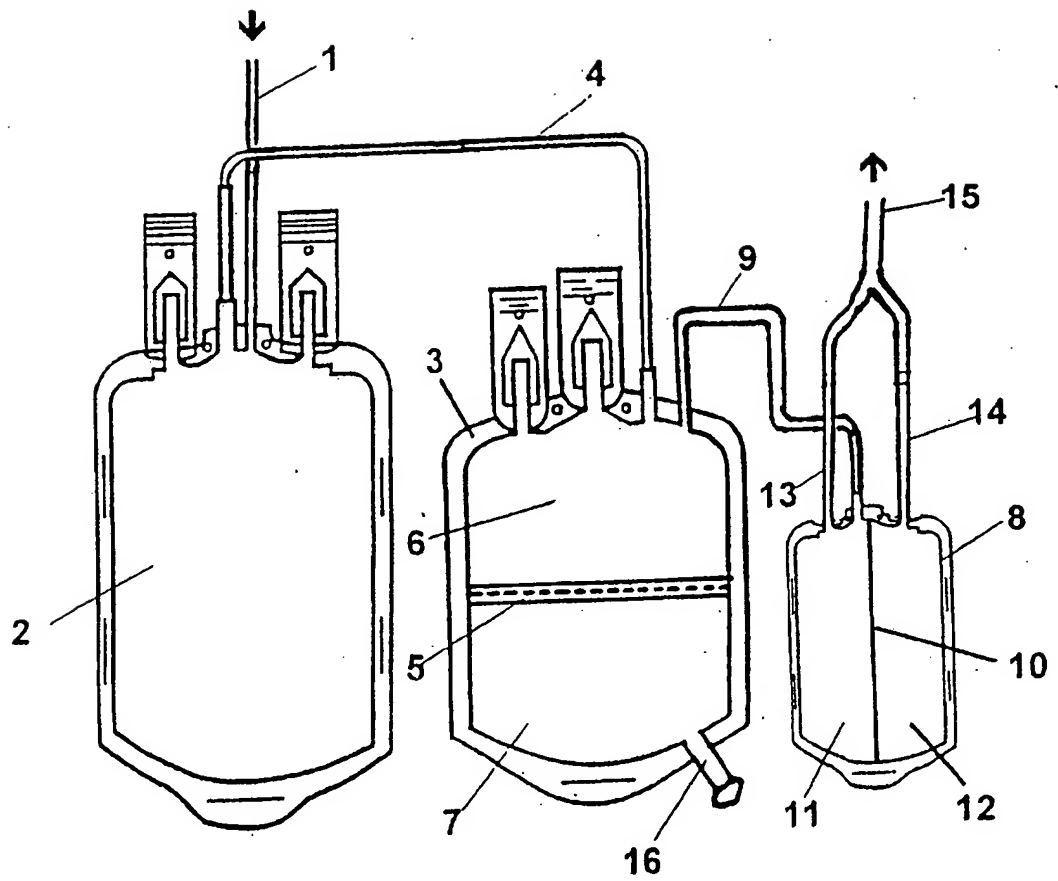
22. System according to Claim 21, characterized in that the bags and the connections are made of anallergic and perfectly sterile plastics of surgical quality.

23. Use of the closed system according to Claim 21 for the preparation of autologous fibrin glue ready to be used, according to the process recited in one or more of Claims 14-20.

5 24. Autologous fibrin glue, when obtained by the process according to one or more of the preceding claims 1-20, and/or by the closed system according to Claims 21 and 22.

25. Use of autologous fibrin glue according to Claim 24 for surgical use, to connect biological components and/or as replacement or integration of surgical sutures

1 / 1



INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/05104

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61L25/00 A61M1/02 C07K14/75

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61L A61M C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 505 962 A (MIRAMED SPA) 30 September 1992 see the whole document ---	1-25
T	WO 96 31245 A (HAMILTON HOSPITALS) 10 October 1996 see the whole document ---	1-25
X	WO 91 16063 A (UAB) 31 October 1991 see the whole document ---	1-25
X	WO 91 09573 A (CRYOLIFE INC.) 11 July 1991 see the whole document ---	1-25
X	WO 86 01814 A (COLUMBIA UNIVERSITY) 27 March 1986 see the whole document ---	1-25
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex

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Date of the actual completion of the international search

6 February 1998

Date of mailing of the international search report

13/02/1998

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/05104

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US 4 714 457 A (R ALTERBAUM) 22 December 1987 see the whole document ---	1-25
A	F H SILVER ET AL.: "Preparation and use of fibrin glue in surgery" BIOMATERIALS., vol. 16. no. 12, August 1995, GUILDFORD GB, pages 891-903, XP000513088 see the whole document -----	1-25

INTERNATIONAL SEARCH REPORT

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